MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, M. Sumtsova st., Sumy 40007, Ukraine
eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua
ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite / Як цитувати статтю: Hlushchenko V, Ivakhniuk T, Oleshko T, Berladir K, Smiyanov V, Oleshko O. Modern approaches and possibilities of application of 3D modeling for tissue engineering and bone regeneration. Literature review. *East Ukr Med J*. 2023;11(4):337-351

DOI: https://doi.org/10.21272/eumj.2023;11(4):337-351

ABSTRACT

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MODERN APPROACHES AND POSSIBILITIES OF APPLICATION OF 3D MODELING FOR TISSUE ENGINEERING AND BONE REGENERATION. LITERATURE REVIEW

In recent decades, polymers and biomaterials (polylactic acid (PLA), polycaprolactone (PCL) and hydroxyapatite (HA)) have created a real alternative in orthopedics, surgery, and cardiac surgery to traditional metals, thanks to the possibility of elimination after the implementation of their function. Progress in 3D design and the possibility of involving 3D printing technologies to create three-dimensional structures makes it possible to bring modern science to a higher quality level. Also, the presence of disadvantages inherent in metal scaffolds, such as discrepancy in mechanical properties, uncontrolled resorption, and lack of biological neutrality of foreign material about bone tissue, due to the possible development of several clinical complications, is the main problem of using degradable alloys in clinical conditions. To eliminate these problems, the following methods are used: the formation of a protective coating, post-cast processing or the development of new alloys, the use of hydroxyapatite instead of metal bases, and the use of 3D printing technologies.

Materials and methods. The author selected more than 50 scientific works from the world literature on the problems on techniques for tissue engineering: fused deposition modeling, 3D printing, 3D bio circuitry, stereolithography, and selective laser sintering.

Results. The development of individual materials that are capable of biodegrading polymers and are biocompatible, alone or in combination with mineral components, makes it possible to obtain materials for 3D printing with mechanical properties and chemical stability suitable for use in bone tissue regeneration. The mechanical properties of the combined scaffolds can be used in the trabecular bone because they correspond to the mechanical characteristics of the latter. The ability to control degradation depends on the composition of the copolymer while demonstrating improvement as a result of the inclusion of mineral phases - hydroxyapatite. After all, HA enhances the degradation of copolymers based on PCl and PLA. The use of these materials during the production of three-dimensional structures by the method of direct 3D printing makes it possible to significantly reduce the consumption of resources and time. The possibility of correcting the framework architecture and porosity leads to the appearance of additional levers of balance and control in the direction of resorption of the nanomaterial, namely the possibility of creating artificial bone.

Conclusions. The data from processed literary sources and the results of a large number of studies allow us to state that the method of direct 3D printing is a priority in the production of three-dimensional porous structures, the basis of which can be natural (collagen, alginates, gelatin and chitosan) and synthetic polymers (aliphatic polyesters, polylactic acid (PLA), polyglycolic acid (PGA), poly-ε-caprolactone (PCL), polydioxanone (PDO)). At the same time, the latter, due to their properties, are more prioritized.

Keywords: Biomaterials, polymers, poly lactic acid (PLA), hydroxyapatite (HA) and polycaprolactone (PCL), tissue engineering, regeneration of bone tissue, fused deposition modeling, 3D printing, 3D bio circuitry, stereolithography, and selective laser sintering.

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СУЧАСНІ ПІДХОДИ ТА МОЖЛИВОСТІ ЗАСТОСУВАННЯ 3D МОДЕЛЮВАННЯ ДЛЯ ТКАНИННОЇ ІНЖЕНЕРІЇ ТА КІСТКОВОЇ РЕГЕНЕРАЦІЇ. ОГЛЯД ЛІТЕРАТУРИ

За останні десятиліття полімери та біоматеріали (полімолочна кислота (PLA), полікапролактон (PCL) та гідроксиапатит (HA)) створили реальну альтернативу в ортопедії, хірургії та серцевій хірургії традиційним металам, завдяки можливості елімінації після реалізації своєї функції. А прогрес в 3D проектуванні та можливість залучення технологій 3D друку для створення об'ємних структур, дає змогу вивести сучасну науку на більш якісний рівень. Також, наявність недоліків, що притаманні металевим скафолдам, таких як: розбіжність механічних властивостей, не контрольована резорбція та відсутність біологічної нейтральності стороннього матеріалу по відношенню до кісткової тканини, в зв'язку з можливим розвитком низки клінічних ускладнень – є основною проблемою використання деградуючих сплавів в клінічних умовах. Для ліквідації цих проблем використовують наступні методи: формування захисного покриття, post-cast обробка чи розробка нових сплавів, використання гідроксиапатитну натомість металевих основ, а також застосування технологій 3D принту.

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Матеріали та методи. У науковому дослідженні проведений огляд літературних джерел щодо методик для тканинної інженерії: 3D-друк, моделювання плавленим осадженням, 3D біосхема, вибіркове лазерне спікання та стереолітографія.

Результати. Розробка індивідуальних матеріалів, що здатні до біологічного розпаду полімерів та є біосумісними, окремо чи в поєднанні з мінеральними складовими, дає змогу отримувати матеріали для 3D принту з механічними властивостями та хімічною стабільністю, що придатні до використання в регенерації кісткової тканини. Механічні властивості поєднаних скафолдів можуть використовуватися в трабекулярній кістці, адже відповідають механічним характеристикам останньої. Можливість контролю деградації залежить від складу кополімеру, при цьому демонструючи покращення в результаті включення мінеральних фаз – гідроксиапатит. Адже, HA посилює деградацію сополімерів на основі PCl та PLA. Використання даних матеріалів під час виготовлення тривимірних структур методом прямого 3D друку дає можливість суттєвого зменшення витрати ресурсів і часу. Можливість корекції архітектури каркасу та пористості призводить до появи додаткових важелів балансу та контролю в напрямку резорбції наноматеріалу, а саме можливості створення штучної кістки.

Висновки. Дані опрацьованих літературних джерел та результати великої кількості досліджень дозволяють стверджувати, що метод прямого 3D-друку є пріоритетним у виготовленні тривимірних пористих структур, основою яких можуть бути природні (колаген, альгінати, желатин та хітозан) та синтетичні полімери (аліфатичні поліефіри, полімолочна кислота (PLA), полігліколева кислота (PGA), полі-ε-капролактон (PCL), полідіоксанон (PDO)). При цьому останні, за рахунок своїх властивостей, є більш пріоритетними.

Ключові слова: біоматеріали, полімери, полімолочна кислота (PLA), гідроксиапатит (HA) і полікапролактон (PCL), тканинна інженерія, регенерація кісткової тканини, моделювання плавленого осадження, 3D-друк, 3D біосхема, стереолітографія та селективне лазерне спікання.

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INTRODUCTION / ВСТУП

The main feature of the third millennium is the desire to improve the quality and duration of human life. Successes in the development and use of new biomaterials, i.e. materials used in medicine to maintain the vital activity and normal functioning of the body, play a significant role in achieving this. Over the last 50 years, more than 40 different materials (ceramics, metals, polymers) have been used to treat, restore, and replace various parts of the human body, including skin, muscle tissue, blood vessels, nerve fibers, bone tissue, etc [1].

The relevance and necessity of developing new biomaterials is due to the high demand for polymeric materials for various fields of activity, primarily biomedical ones [2].

The development of new materials for medical purposes, necessary for the contact of a living organism with the environment, is a task of high complexity. Specialized biocompatible materials are especially in demand for the new direction of medical materials science, formed in recent years – cellular and tissue engineering, related to reconstructive surgery and the development of bioartificial organs. These studies are implemented at the intersection of the chemistry of high-molecular compounds, biotechnology, biophysics, molecular and cellular biology, and medicine and contain a complex of interconnected fundamental tasks [3-5].

As a result of the rapid progress of various constituent parts of physic-chemical biology, a new direction in science and production emerged, which was named biotechnology. This direction has been formed over the last two decades and has already gained powerful development. Knowledge about life processes, which is rapidly expanding, allows not only to adapt these processes for practical purposes, but also to manage them, as well as to create quite promising in practical terms new systems that do not exist in nature, although like existing ones [6-8].

Biotechnology in general is a system of techniques for the targeted use of vital processes of living organisms to obtain industrially valuable products. These technologies are based on the use of the catalytic potential of various biological agents and systems – microorganisms, viruses, plant and animal cells and tissues, as well as extracellular substances and cell components. Currently, the development and development of biotechnology occupy an important place in the activities of almost all countries [9].

Biotechnological processes are multifaceted in their historical roots and in their structure, they combine elements of fundamental sciences, as well as a number of applied fields, such as chemical technology, mechanical engineering, economics. Modern biotechnologies are in dire need of scientifically based development of technology and hardware design. Therefore, an organic connection with technical sciences is necessary: mechanical engineering, electronics, automation. Social and economic sciences are also important in the development of ecological biotechnology since the practical tasks solved by it have great socio-economic significance for any society [10-12].

Biomaterials and polymers (HA, PLA, and PCL) in recent decades have become a real alternative to traditional metals in orthopedics, surgery, and cardiac surgery due to the possibility of complete elimination after performing their function. And the possibility of creating 3D structures takes modern science to a completely different level. However, the presence of a number of disadvantages characteristic of metal structures, such as uncontrolled resorption, discrepancy in mechanical properties (Young's modulus, etc.), as well as the lack of absolute biological neutrality of foreign material in relation to bone tissue, is the main problem of the clinical use of degrading alloys, in connection with the possibility of the development of a number of clinical complications. To eliminate this problem, various methods are used: creating new alloys and post-cast processing, forming a protective coating, or replacing the metal base with a hydroxyapatite one, as well as the use of 3D printing technologies [13–16].

MATERIALS AND METHODS

The author selected more than 50 scientific works from the world literature on the problems on techniques for tissue engineering: fused deposition modeling, 3D printing, 3D bio circuitry, stereolithography, and selective laser sintering.

RESULTS AND DISCUSSION

Bone is a polymer matrix with a composite structure consisting of hydroxyapatite crystals [1], And the cause of its damage can be injuries, oncological diseases of bone tissue, fractures, osteoporosis and others. That is why the reconstruction of damaged bone tissue is an urgent problem in the field of orthopaedics. Until a certain time, autografts, allografts and xenografts were the most commonly used methods. However, it is now known that their use is accompanied by difficulties in limiting disease transmission, the emergence of an immune system response, and is characterised by insufficient biocompatibility and donor problems [14].

An alternative method of bone restoration today is bone tissue engineering. The main task of modern tissue engineering is the creation of a porous three-dimensional structure that imitates the extracellular matrix with the preservation of biological and mechanical properties, the so-called framework. It should be biodegradable, biocompatible and have sufficient mechanical strength, interconnection with bone tissue and porosity [3]. Traditional methods can create highly porous scaffolds, but they have limitations in designing internal scaffolds and producing reproducible interconnected porous structures for nutrient diffusion, cell migration and growth, and cellular waste removal. Rapid prototyping technologies have provided unparalleled progress in the production of pre-engineered tiny porous structures with arbitrary internal structure, which is a promising method for the fabrication of scaffolds with suitable mechanical and biological properties for bone regeneration. These methods are based on creating objects layer by layer according to the 3D project. Fused filament fabrication (FFF) is a relatively inexpensive rapid prototyping technique that is widely used to produce desired scaffolds, with a completely controlled structure of the latter, both externally and internally [15]. To obtain a 3D pattern directly from an automated design model, the FFF filament is melted in a thinner chamber and deposited layer by layer through a nozzle. The print head is raised after each step and the next layer is applied on top of the previous one until the object that has been designed is complete. [16].

Choosing the right material (biocompatible, biodegradable, and bioactive) plays an important role in the manufacture of a bone framework that meets all the necessary requirements. A wide range of polymers are used for tissue engineering: natural (chitosan, collagen, hyaluronic acid, etc.) and synthetic (PGA, PLA, PLGA). Although natural polymers have more distinct properties for enhancing bone regeneration, their disadvantages, such as insufficient mechanical properties, and immunogenetic response, limit their application in bone tissue engineering. Therefore, the use of synthetic polymers is an alternative for the treatment of bone defects. Synthetic polymers have several advantages, such as greater durability, individual mechanical properties, and reproducibility. In addition, the advantage of synthetic polymers is their heat resistance, which makes them suitable for the production of fusible filaments [17].

Due to the rapid development of the additive manufacturing industry, which includes 3D printing, customised medical devices with high geometric accuracy can be manufactured relatively quickly. However, the scientific development and search for materials with specific properties is still in progress, including those that are adapted for improved bone repair. Materials with individual properties close to bone tissue and, importantly, that can serve as a temporary support, allowing new bone tissue to grow in while the material resorbs, are being searched for. Thus, controlling the degradation rate of bone implant materials can promote bone healing by balancing between implant resorption and new tissue formation [15, 16].

The search for the ideal materials for reconstruction has always been a challenge for orthopedic surgeons and scientists. According to the characteristics of the components, synthetic materials for bone restoration can be divided into metals and their alloys, composite materials, calcium phosphate bone cement, bioceramics, tissue engineering materials, polymeric materials, etc. Among them, polymeric materials have been used for bone reconstruction since the mid of the 20th century, with the advantages of reference biocompatibility and immunocompatibility [18]. Polymeric materials used in bone tissue engineering research can be divided into synthetic and natural polymeric materials. The natural polymers include fibrin, collagen, sodium alginate, chitin, chitosan, hyaluronic acid, etc. [19, 20]. Synthetic polymers include PGA, PLA, polycaprolactone (PCL), poly(lactic-coglycolic acid) (PLGA), polyamide polyvinyl alcohol (PVA) and other synthetic polymers [21]. Natural polymeric materials have good biocompatibility and thus contribute to improved cellular properties. However, they are difficult to engineer, have limited processing capacity, have a high risk of contamination, and are characterized by instability and variability. Compared to synthetic, natural materials, polymeric materials have stable chemical properties and can be modified to obtain specific properties. Other advantages of synthetic polymeric materials include cost-effectiveness, longer storage time, and mass production capacity [22]. Synthetic polymeric materials are mainly used in the form of scaffolds to restore bone structure, and composite materials with growth factors, tissue cells and other materials, and thus can improve the biocompatibility of the material and biological activity. The development of biomaterials offers great prospects for the future treatment of bone diseases and injuries, and scientists from around the world are constantly researching biomaterials that can repair bone defects [23].

Over the past few decades, the combination of high-resolution imaging and additive manufacturing has enabled the development of customised implants and surgical devices [24]. Scientists led by K. Tappa have confirmed that the successfulness of an implant depends on the type of biomaterial used for its manufacture. The ideal material for an implant should be biocompatible, mechanically strong, inert, and easy to mold. The ability to create customized implants for patients with bioactive drugs, proteins, and cells has made 3D printing technology revolutionary in medicine and pharmaceuticals. Currently, various biomaterials are used in medical 3D printing, and ceramics, composites, including metals, and polymers. Thanks to continuous progress and research in the field of biomaterials used in 3D scaffolding, there has been a rapid increase in the use of 3D printing to manufacture customized implants, scaffolds for drug delivery, prostheses, and regenerative medicine and 3D scaffolds for tissue engineering. A detailed analysis of the most common types of medical 3D printing technologies, extrusion-based bioprinting, including fused deposition modeling, inkjet, and their clinical applications, and poly jet printing, the different types of biomaterials currently used by the identification , and researchers of the main limitations in their use, allows us to choose the most optimal type of implant for each specific case [25].

Due to the short processing time and relatively low cost of producing fused filaments (fused filament fabrication – FFF), 3D printing is an attractive technique for manufacturing medical devices. This technique produces 3D objects by melting thermoplastic polymer filaments, extruding them through a heated nozzle, and applying the molten materials to a build plate with high geometric accuracy [25, 26]. Researchers have focused on the development of new synthetic materials with good printability for use in tissue engineering. In this regard, biocompatible materials have attracted much attention [15]; this applies to thermoplastic polyester. Polymer-based scaffolds aimed at regenerative bone tissue engineering should become temporary scaffolds with the potential to promote bone regeneration. Degradable materials that support the formation of new bone tissue during their active or passive resorption without causing harmful effects on bone healing, such as excessive inflammatory response, have gained great popularity and relevance [27].

PLA is one of the thermoplastic polyester used in clinics as a resorptive support material for bone and ligament fixation [28], which is of great interest for the purpose of producing fusion filaments due to its good ductility, printability, biodegradability and biocompatibility. It also has a relatively high level of mechanical properties and can be made from renewable resources such as corn [29, 30]. PLA is hydrolysed in vivo to form lactic acid [31]. Due to its properties, PLA has been received by the US Food and Drug Administration for widespread clinical use. However, this material also has the following disadvantages: high hydrophilicity and high degradation rate, and degradation intermediates can lead to an oxidation of the pH of the medium, as well as its Young's modulus differs significantly from that of living bone, because the material itself is quite brittle. PLA as a material directly used for bone repair is not ideal, and to optimise its properties, other materials need to be added to create a perfectly balanced polymer [32].

Notwithstanding the degradability and biocompatibility of PLA, its biological activity is insufficient, so the development of composite materials that include a mineral component similar in composition to bone tissue is an urgent problem of modern science. For example, HA, which is a mineral component of bone tissue, has been found to develop the bioactivity of the substance [33-35]. HA itself has biocompatibility and bioactivity, so it can stimulate bone growth by stimulating cell adhesion [7]. However, both of these substance (PLA and HA) are fragile [29, 33], which limits their application to bones that bear loads. To increase plasticisers, strength, rigid fillers and copolymers can be added to produce a polymer composite that can have improved mechanical properties of materials [29, 30]. For example, polycaprolactone, which is a bioresorbable and biocompatible polyester with promising properties for medical scaffolds, has been reported to improve the strength of brittle PLA, which could lead to a polymer matrix more suitable for bone tissue engineering applications [7, 29]. A group of other scientists investigated the role of hydroxyapatite on the properties of PCL scaffolds for bone implants [12]. Previously designed porous scaffolds (400 µm pore size and 37 % porosity to enhance bone regeneration) were fabricated using commercial FFFs. First, hydroxyapatite was synthesised and then composite films with different percentages of HA (0 %, 5 %, 10 %, 15 % and 20 %) were fabricated to maintain the biological and mechanical properties of the experimental material in comparison to the structural components of bone. The range of hydroxyapatite percentages was chosen based on rheology and the ability to print the filaments. After the fibres were fabricated, scaffolds were printed from the prepared composite films and the effect of different hydroxyapatite ratios on the biological and mechanical properties of the scaffold was investigated. The scaffolds showed better mechanical properties compared to some previous studies. In addition, their biological and bioactivity properties reached the desired level. And the use of an inexpensive device for manufacturing scaffolds allows us to reduce the final price of scaffolds, which is a very important factor in the development of medical instruments and their accessibility to everyone. Thus, PCL/HA scaffolds printed on a 3D printer are promising for bone tissue engineering [16, 29, 35].

Polycaprolactone (PCL) is a polyester organic polymer made by artificial synthesis. At physiological temperatures, semi-crystalline PCL reaches an elastic state, resulting in its high strength, excellent mechanical properties, and, high toughness, as well as crystallinity, slow degradation rate, and good biocompatibility [36]. In addition to its biocompatibility and biodegradability, PCL is widely used as a substrate for absorbable sutures, regenerative therapies and drug delivery scaffolds due to its readily available and cost-effective nature. The longer degradation time contributes to the widespread use of the latter for the replacement of hard and load-bearing tissues by increasing their stiffness, as well as for the replacement of soft tissues by reducing their molecular weight and degradation time [22]. In order for the scaffold to have antibacterial properties, Felice et al. prepared scaffolds mixed with zinc oxide. The results showed that a high concentration of zinc oxide can cause early mineralisation, and adjusting the concentration of zinc oxide and its distribution in the material helps to regulate the degradation rate of the material, which exhibits antibacterial properties against S. aureus [37]. Lee et al. in their research cultivated nanoparticles on a polyhexylactone scaffold coated with polydopamine. It was found that this scaffold composition has good osteogenic activity in in vivo experiments, which is expected to provide new options for materials for the repair and regeneration of bone defects [38]. Other scientists made 3D-printed calcium silicate, acellular extracellular matrix, and PCL scaffolds and observed that they demonstrated cell adhesion, excellent biocompatibility, differentiation, and proliferation by increasing the expression of osteogenesis-related genes [39]. The microporous matrix of the PCL scaffold supports osteoblast attachment, osteogenic differentiation, and proliferation, while the multilayer polyelectrolyte fixation on the surface of the endospores supports local release of dexamethasone. These microporous scaffolds demonstrate the ability to deliver dexamethasone topically and promote the differentiation and proliferation of osteoblastic cells in vitro [40].

The rate of degradation and by-products of biomaterials are of primary importance for tissue regeneration. Degradation can occur actively under the influence of cellular activity and the intercellular environment at the implantation site, or passively, due to the physicochemical properties of the biomaterial itself [41, 42]. The rate of polymer degradation depends on several factors, the main ones being molecular weight, degree of crystallinity and porosity, or surface area [43]. Environmental factors that can play an important role in the degradation of the scaffold include temperature, pH, and the presence of mechanical irritants. For example, the in vivo degradation rate of PLA has been reported to be in the range of 12 months to 5 years, depending on the degree of crystallinity [44]. As a rule, PCL shows a lower degradation rate than PLA, which is up to four years under certain conditions [25]. However, it is possible to increase the degradation rate of polymers by adding mineral phases such as hydroxyapatite [45].

Recent studies have highlighted the development of customised composites and polymer blends [36], including their application in the fused filament fabrication technique [37-40]. Most studies have focused on the combination of polymer matrices with bioactive minerals to improve their, bioinertness, bioactivity and degradation. Previous work has focused on combining PLA with hydroxyapatite or polycaprolactone with HA or similar calcium phosphate-based ceramics. Although the use of PCL has been widely investigated using other additive manufacturing techniques, there is a lack of research that has investigated the combination of PLA and PCL with HA using the direct 3D printing technique with FFF filaments, as well as the degradation characteristics of such a combination. This new approach to the production of FFF filaments has a lower cost, and thus can serve as an alternative to improve not only the development of individual geometrical characteristics for each patient, but also to customize their physicochemical characteristics to improve adaptation to the implant site. For example, mechanical properties that are adjusted depending on the composition and structure of the final scaffold or composite are an alternative when choosing a defect replacement method depending on the bone type [46].

Polycaprolactone and hydroxyapatite were chosen as the materials for osteoimplant scaffolds in the study by Rezania et al [22]. The positive characteristics of PCL, long-term biodegradability, including biocompatibility, excellent FDA approval, and mechanical properties for widespread clinical use, make it a suitable material for bone tissue engineering [14, 41, 47]. In addition, it is also suitable for printing with an FFF device [48-51]. HA is a bioactive and biocompatible mineral structure similar to natural bone tissue, which is widely used as a bone substitute. Recently, polymer-ceramic compositions such as PCL/HA have been used to create a bone skeleton that enhances bone regeneration and cell proliferation in vivo. It should be noted that the Young's modulus of the resulting material differs from that of human bone [51].

A number of papers have been published on the fabrication of 3D-printed composite bone skeletons. Although they have shown sufficient results, there is a lack of in vivo studies in their work [51].

Kim J-W, et al. fabricated porous PCL/ HA composite scaffolds for bone regeneration, which can have a specialised macro/microporous structure with excellent in vitro bioactivity and high mechanical properties by printing using a range of solvents. The effect of hydroxyapatite ratio (0, 10, 15 and 20 %) on the biological and mechanical properties of scaffolds fabricated using a 3D printing system was evaluated and it was shown that this process resulted in highly porous scaffolds (78 % porosity) with a pore size (~248 μm), which was typical for all PCL/HA composite scaffolds and promoted bone regeneration. Mechanical properties, such as tensile strength and yield strength in compression, increased with the increase of HA content. In addition, the introduction of bioactive HA particles into PCL polymer led to a significant improvement in the ability to form apatite in vitro. Thus, it was proved that the addition of HA particles increased the mechanical properties (tensile and compressive strength) and good bioactivity. Despite the FFF method, which is based on melting and extrusion of filaments, the 3D printing system uses air pressure to extrude the material [4].

Bruyas A. et al. investigated the effect of composition (0-60 % β-TCP/PCL) on the properties of scaffolds produced by FFF. This work was aimed at the experimental characterisation and development of 3D printed scaffolds for potential orthopaedic applications. It was shown that the surface roughness and wettability were directly and inversely proportional to the amount of β-TCP, and the degradation rate increased with the amount of ceramic. The addition of β-TCP enhanced proliferation and osteogenic differentiation. The effect of porosity and composition on the mechanical properties of the 3D-printed scaffold was also systematically studied. Both the increase in the amount of β-TCP and the decrease in porosity increased the Young's modulus of the 3D-printed scaffolds. Thus, the increase in β-TCP improved the biological, mechanical, degradation, and surface properties of the bone scaffold. However, they did not investigate the bioactivity of the samples and the rheological behavior of the printed samples [52].

In their article, Huang et al. investigated the use of polymer-ceramic scaffolds for bone tissue engineering. Different ceramic materials (hydroxyapatite and β-tri-calcium phosphate) were mixed with poly-ε-caprolactone. The scaffolds with different material compositions were manufactured using an extrusion-based additive manufacturing system. The produced scaffolds were chemically and physically evaluated, including mechanical testing, wettability, scanning electron microscopy, and thermogravimetric testing. Cell viability, proliferation, and attachment tests were performed using human adipose-derived stem cells (hADSCs). The results show that HA-containing scaffolds exhibit better biological properties and TCP scaffolds have improved mechanical properties. However, the addition of these two ceramic particles did not affect the wettability of the scaffolds [53]. Gatto M. L. et al. reported 3D-printed polycaprolactone / hydroxyapatite scaffolds (70/30 % wt) for bone tissue engineering. They prepared a PCL/HA powder blend and used laser powder bed fusion (LPBF) technology to fabricate scaffolds. They evaluated the scaffolds' morphological properties, porosity, mechanical and biological properties [54].

Using optimised LPBF printing parameters, micro- and macroporous scaffolds for bone regeneration were fabricated by regularly repeating diamond (DO) and rhombic dodecahedron (RD) unit cells in space. After fabrication, the structural, mechanical, and biological characteristics of the scaffolds were evaluated. The interaction of scaffolds with human mesenchymal stem cells (hMSCs) allowed us to study the degradation processes of the PCL matrix. The biomechanical properties and biodegradation of the scaffolds were compared with the results of the literature and bone tissue data. Mechanical compression tests, biological viability up to 4 days of incubation, and degradation rates showed a strong dependence of scaffold behaviour on the geometry of the unit cell as well as on global geometric features. The study of the combination of biocompatible polymer matrices with a bioactive mineral such as HA to provide individual characteristics to materials for the manufacture of fusion filaments is a relevant and very important area of bone engineering development. The study of the combination of these materials allows adjusting the property settings to produce materials suitable for use in bone repair, with a particular focus on their degradation behaviour, including mechanical and chemical resistance [55, 56].

It is known that the blending of PLA and PCL makes it possible to obtain a porous morphology for the blends, and the minor component in the polymer blend most often forms a dispersed phase in the continuous phase formed by the major component. In contrast to PLA/PCL scaffolds, composite blends with HA showed a rough surface caused by the mineral phase incorporated into the polymer matrix. Thus, the incorporation of HA can not only improve the bioactivity of the material, but also increases the surface roughness, which may also have a beneficial effect on cell adhesion and proliferation [24, 49-52].

The thermal properties (Tg, Tm, and Tdeg) of blends and composite blends were between the values of the input pure polymers, and the blending phenomenon of both polymers could be confirmed. The degradation temperatures for the blends and composite blends also confirmed that the addition of polycaprolactone improved the thermal stability of PLA. However, the decrease in Tcc with increasing polycaprolactone content may be due to the nucleation effect attributed to polycaprolactone during PLA crystallization [57].

According to Akerlund et al., along with improved thermal stability, an increased onset temperature and degradation shift were observed for both blends and composite blends compared to pure PLA [53]. The attribute this decrease to the hydrolysis of PLA, which was most likely initiated by HA, as it is a hydrophilic compound with a high affinity for moisture. Hydrolytic chain breakage is the most common degradation pathway for high molecular weight complex polyester such as PLA and can occur via two different main routes such as bulk or surface degradation. The former results in a decrease in the molecular weight of the polymer due to the release of end hydroxyl and carboxyl group by-products. During the latter surface degradation, the molecular weight remains unchanged due to surface by-products that leave the surface by diffusion into the medium, which in turn leads to a liquefaction of the material [33]. However, since this decrease in the initial decomposition temperature was not observed for the composite blends in the study by Akerlund et al. it can be assumed that this improvement is due to the addition of PCL. In general, thermal stability studies have shown that neither extrusion nor printing temperature had any effect on these materials [53]. This was further confirmed by the results obtained using FTIR on materials such as film or filament, where no changes in chemical composition were detected. This is of great importance in the development of materials for biomedical applications, as changes in chemical composition can trigger harmful responses in the body, such as strong immune reactions [58].

According to the published results of Nishida et al., the general trend observed in the mechanical properties of blends and composite blends was a decrease in stiffness with increasing PCL content, i.e., an increase in the amount of PCL increased the plastic properties of the materials. A study of the effect of PCL content in PLA:PCL blends on Young's modulus and peak compressive strength showed that for the two blends with more PCL, the compressive stress decreased with increasing PCL content [59]. Although the general trend was for the compressive strength to decrease with increasing PCL content, the 90PLA10PCL blend resulted in a lower compressive strength value than the 80PLA20PCL and 70PLA30PCL blends. Nevertheless, both the treated blends and the composite blends demonstrated higher mechanical properties than native trabecular bone, but not cortical bone, indicating a possible application as a support material for high load bearing cancellous bones [49].

In addition, another study examined the effect of filling density on the compressive strength of pure PLA cylinders printed on a 3D printer. The researchers reported a fracture load of 21 kN for cylinders with 80% filling [57], the same compressive failure load as that obtained for pure PLA with 100% filling density in another study. This means that a similar resistance to compression load can be obtained with a 20 % lower filling density. This statement can be further investigated with composites and blends to minimize the amount of used material [59, 60].

Morphological analysis and weight loss showed a slower degradation rate of polycaprolactone compared to polylactic acid, which is due to the hydrophobic nature of PCL and higher crystallinity [18, 8, 37]. Interestingly, in accordance with previous studies, PLA: PCL copolymers showed higher degradation rates than pure polylactic acid. In general, PLA: PCL blends degrade about 10% faster than polylactic acid. This phenomenon can be explained by the plasticizer effect from the addition of PCL, which disrupts the crystallization of polylactic acid, thus morphing PLA and enhancing its degradation. Changes in the surface morphology of the PLA: PCL blends may also have played a role in the higher degradation rates compared to pure polylactic acid. It is known that the morphology of the mixtures reflected higher roughness with the appearance of pores, the size of which increased with increasing PCL content [58]. This morphology can increase the total surface area of materials and their wettability, thus promoting faster degradation. Finally, the addition of HA further improved the degradation behavior, providing 40% faster degradation compared to PLA. It should be noted that the incorporation of hydroxyapatite into polymer matrices can increase the overall hydrophilicity and decrease the crystallinity of PLA [24, 56], thus increasing the degradation rate. Degradation of the surface was noticeable by the decrease in the diameter of the cylinders, which was approximately 0.5 mm for the mixtures and 2 mm for the composite mixtures. Surface degradation was also analyzed by SEM; the smooth surface of the primary samples even after 6 hours of degradation became rough after 28 days due to erosion. It is also possible to see some differences in the surface morphology between the different blends, which according to Mohseni et al may be a consequence of the different rates of the hydrolysis reaction for the blends [11, 26, 33].

In their study, Olewnik-Kruszkowska et al. studied the thermal properties of samples analyzed by DSC, comparing pristine and degraded samples. As a rule, a decrease in Tcc and a break in the melting curves for degraded samples were found. A lower Tcc correlates with a decrease in overall crystallinity and molecular weight [55]. Similarly, the formation of shorter chains during degradation can lead to the formation of a double peak in the melting curves, depicting the first peak for the primary polymer structure and the second peak for the new crystal structure. In addition, the composite blends showed a decrease in Tg during degradation, as a potential result of PLA degradation, leading to an increase in lactic acid oligomer byproducts, as also evidenced by XRD analysis [15].

PCL was found to increase the thermal stability of non-degraded materials. This may also explain the increased thermal stability of the composites after degradation. Since the degradation of PLA was accelerated by the addition of the mineral, the relative content of PCL increased compared to PLA in the original composition. However, the decrease in thermal stability of the two blends with higher amounts of PLA after decomposition may be due to the decrease in molecular weight [58].

In general, individually formulated filaments consisting of combinations of polylactic acid, polycaprolactone, and hydroxyapatitedemonstrated thermal and chemical stability. Also, these materials showed very good properties necessary for printing in order to use them in the economical FFF technique [54]. Further characterization of the degradation of the materials and the by-products released during the degradation is necessary to evaluate the safety of these materials from a biological point of view and to further investigate their potential as materials for tissue engineering of bone defects. Importantly, the degradation behavior can be controlled by incorporating both PCL and HA into PLA. By carefully controlling the amount of PCL, the degradation rate can increase up to 10%, while the further addition of HA contributes to a 3-fold faster degradation compared to pure PLA, or 1.5-2 times for PLA: PCL blends. These indicators can be further optimized by adjusting the porosity during 3D printing and the overall geometry of the framework. The development of special combinations of materials consisting of biodegradable and biocompatible polymers, in combination with mineral parts or alone, will allow printing materials with chemical stability and mechanical properties similar to living bone [61].

Therefore, in comparison with traditional metal implants used in orthopedics and surgery, biodegradable polymer scaffolds have optimal mechanical parameters from a biological point of view and simplicity in clinical application. However, the problem of uncontrolled premature degradation does not allow the use of these materials, and the available commercial products are unavailable for public medicine and are not available in Ukraine. Optimization and control of polymer degradation terms is possible due to the creation of biological copolymers that have a prolonged degradation term and are biocompatible. Considering the possibility of using polycaprolactones as alternative biomaterials, it is necessary to investigate a number of their features. Namely, the physicochemical properties and biological response of a single polymer, and the change or dependence of the aforementioned functions depending on the ratio of the percentage component of individual polymers when creating combined multicomponent biodegradable polymer scaffolds. Separately taken synthetic polymers have optimal physicochemical parameters, but at the same time they do not have an adequate biological response or vice versa. At the same time, nano-hydroxyapatite (nanoHA) is a material widely used due to its biocompatibility, similarity to the inorganic structure of bone, and direct stimulating effect of osteogenesis. However, there is a problem of creating three-dimensional structures of a clear shape with optimal mechanical parameters based on nano-GA. Therefore, in most cases, the latter is used as a functionalized coating of metal implants, which in turn have several disadvantages. The lack of biodegradation of metals and uncontrolled resorption, the discrepancy in mechanical properties (Young's modulus, etc.), as well as the lack of absolute biological neutrality of a foreign material in relation to bone tissue, the probability of rejection of a monolithic structure, is the main problem of the clinical use of metal alloys, in connection with the possibility of developing a number of clinical complications or even the need for repeated surgery [16, 27, 62].

Considering this, the creation of biodegradable polymer-nano-hydroxyapatite scaffolds with nanoparticles and the determination of their physicochemical properties and biological response is an urgent and not fully resolved problem today [55].

In recent years, several techniques have been used for tissue engineering: fused deposition modeling, 3D printing, 3D bio scheme, stereolithography, and selective laser sintering. 3D printing is the optimal method of processing polycaprolactones, because the main question regarding the application of the processing of polymeric biomaterials is usually the method of their processing. However, it is 3D printing that has become an inspiring technology to produce three-dimensional porous biomaterials for replacing damaged hard tissues and repairing bone defects. However, not all materials can be used as a basis for 3D printing due to the presence of certain limitations: processing temperature, biocompatibility, biodegradation, appropriate mechanical strength and low cytotoxicity. At the same time, today there are methods of both direct and indirect 3D printing, and the latter also has several disadvantages: the complexity and high cost of equipment, the additional use of toxic solvents, as well as the long-term and multi-stage method, and most importantly – the inability to create a porous structure [49, 52].

CONCLUSIONS / ВИСНОВКИ

A general trend for the mechanical properties of copolymers and composite blends is a decrease in stiffness with increasing PCL content. For the two mixtures with higher PCL content, the compressive stress decreases with increasing PCL content. Additionally, there is a theory about the effect of filler density on the compressive strength of pure PLA 3D-printed cylinders. Thus, a crushing load of 21 kN is reported on cylinders at 80% filling, the same compressive crushing load of PLA at 100% density. This means that similar compressive load resistance can be obtained with a 20% lower filler density. This trend should be further studied and confirmed.

Hydrolytic chain cleavage is the most common degradation pathway for high molecular weight polyesters such as PLA and can occur via two different main pathways such as bulk or surface degradation.

Weight loss and surface morphology analysis indicated slower degradation of PCL compared to PLA, which correlates with PCL's hydrophobic nature and higher crystallinity. Interestingly, PLA: PCL blends degrade 10% faster than pure PLA. The surface morphology of copolymers is characterized by greater roughness with the appearance of pores that increase in size with increasing PCL content. This feature is not confirmed.

Finally, the addition of hydroxyapatite to the copolymer structure accelerates the degradation rate by 40% compared to pure PLA, by increasing the overall hydrophilicity and decreasing the crystallinity of PLA.

Therefore, the analysis of literary sources shows that the combination of PLA and PCL leads to the formation of a porous surface, but also the structure of the scaffolds, according to the statement that the minor component in the mixture of polymers most often forms a dispersed phase in the continuous phase formed by the main component. In contrast, composite mixtures have a rough surface caused by the mineral phase incorporated into the polymer matrix. Thus, the inclusion of HA in the base of the matrix not only increases the bioactivity of the material but also increases the surface roughness, which can also favorably affect cell adhesion and proliferation when osteoblasts are cultivated on the surface and in the structure of the scaffold.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Today, the question remains open regarding the optimal parameters of the 3D printing process (temperature, PCL/PLA ratio, and metric parameters of pores and printing fibers) and the possibility of controlling biodegradation, optimal concentrations of hydroxyapatite considering the features of its nanostructure as a stimulator of osteogenesis, as well as studying the biological response application of the proposed complex as a whole.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

This paper was supported by the grant from the Ministry of Education and Science of Ukraine (0122U000770), Erasmus + Jean Monnet grant 620717-EPP-1-2020-1-UA-EPPJMO-MODULE.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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Received 24.11.2023
Accepted 10.11.2023

Одержано 24.11.2023
Затверджено до друку 10.11.2023

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